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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,021	03/16/2001	Hubert Metzner	06478.1452	5147

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EXAMINER	
MELLER, MICHAEL V	
ART UNIT	PAPER NUMBER
1655	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/809,021	METZNER ET AL.	
	Examiner	Art Unit	
	Michael V. Meller	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24,27-30,33 and 49-61* is/are pending in the application.

4a) Of the above claim(s) *20-24,27-30 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Any rejection not reiterated herein is hereby dropped.

Election/Restrictions

The restriction of record is maintained. Claims 20-24, 27-30, 33 are withdrawn for the reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising thrombin, benzamidine or p-aminobenzamidine, NaCl or CaCl, l-histidine, mannitol, na, succinate, na lactate, l-arginine, does not reasonably provide enablement for any and all substances, inhibitors of thrombin, sugars, sugar alcohols, amino acids, etc.. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification as filed, is enabled for a composition comprising thrombin, benzamidine or p-aminobenzamidine, nacl, cacl, l-histidine, mannitol, na, succinate, na lactate, l-arginine, but is not enabled for any and all substances, inhibitors of thrombin, sugars, sugar alcohols, amino acids, etc...

The art of biotechnology is a highly unpredictable art and it would be an undue burden for one of ordinary skill in the art to test any and all buffer substances, inhibitors of thrombin, sugars, sugar alcohols, amino acids, etc., to see if they could perform the disclosed use. The term buffer substances is especially broad because this encompasses just about anything. It does not get much broader than the use of the term, "buffer substance". Further, the inhibitor of thrombin is also very broad. There are only two inhibitors enabled for in the specification (benzamidine or p-aminobenzamidine) and only knowing these two inhibitors is simply too broad. There is no way of knowing how one could actually define this class of compounds by just disclosing these two specifically. Applicant has not disclosed enough information to make it clear to one of ordinary skill in the art that all thrombin inhibitors would work in this invention with only knowing the two specifically disclosed inhibitors.

Applicant has only shown in their examples that a composition comprising thrombin, benzamidine or p-aminobenzamidine, NaCl or CaCl, l-histidine, l-arginine, mannitol, na succinate, or na lactate even works for the disclosed use. With only knowing these specific components it is clear that such broad claims are not enabled by

the instant specification when one of ordinary skill in the art is only given the particular components to produce a composition able to perform the disclosed use.

Applicant has argued that there is no undue experimentation for one of ordinary skill in the art to test to see if all of the ingredients in the claimed composition would work in the claimed composition. Applicants themselves have argued that the stability and the activity of the enzymes and components in the preparation are critical and specific to the success of the preparation claimed and at the same time state that anyone of ordinary skill in the art could use any sugar, sugar alcohol, amino acid, non-covalently binding inhibitor of thrombin activity, buffer substances, etc. to make and use the claimed invention. The question is can one of ordinary skill in the art make and use the claimed invention. The answer is simply no.

Knowing only the specific sugars, inhibitors as claimed leads one to what is enabled as set forth above, but it does not lead one of ordinary skill in the art to make and use any and all sugar, sugar alcohol, amino acid, non-covalently binding inhibitor of thrombin activity, buffer substances, etc. to arrive at applicant's specifically claimed preparation containing specific activities and stabilities that are characteristic, as applicant contends, to the specific thrombin preparation claimed. Applicant cannot have it both ways. Either the activities do not matter or they do. Applicant has argued that they are critical and as such one of ordinary skill in the art would not know hot to make and use all of the claimed possible sugar, sugar alcohol, amino acid, noncovalently binding inhibitor of thrombin activity, buffer substances, etc. to arrive at applicant's

specifically claimed preparation containing specific activities and stabilities that are characteristic, as applicant contends, to the specific thrombin preparation claimed.

Claims 49-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification for "measured by a coagulation test with a fibrinogen substrate, is more than 70 %" as claimed in claim 49, for example. Applicant argues that there is support but there simply is not. Each of the "more than" percentages of claims 49-54 have no support in the specification either. Specific ranges are shown in the specification but not the language "more than 90 %", for example. The support that applicant claims is in the specification is not there. The specification states that the thrombin activity is over 70-80 % of the initial level. In other words, 70-80 % over less than what was initially measured. Applicant has taken this to mean more than 70-80 % but that is not what the specification says.

Applicant argues that there plenty of disclosure to support the open ended range of 70% and up but such a range of 70 % - 100 % simply does not exist in the

specification. Isolated points may be in the tables, but nothing which supports such as range of 70 %-100 %.

There is no support for "sugar alcohol at a maximum concentration of 2% (w/v)". There is support for specific amounts of mannitol but not this as claimed. The mannitol is used at 1 and 2 % amounts but that does not provide support for , "sugar alcohol at a maximum concentration of 2%". Nowhere in the specification can such support be found. Applicants comments are noted but the concentration of mannitol used is simply randome points, no where in the specification does it ever suggest that one can only use the sugar alcohols at a maximum concentration of 2 %.

Disclosing simply two isolated points of 1 % and 2 % does not provided adequate disclosure for "at a maximum concentration of 2 %". Applicants argue that the office's standards are too high but that in and of itself is not sufficient. There is no range provided for by the specification of a maximum concentration of 2%. Such ranges are being created after the fact by applicant, after the invention was made, not at the time the invention was made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 49-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allary et al. or Lorne et al. in view of Hanada et al., Brezniak et al. and Altshuler.

Allary and Lorne each teach that thrombin is eluted off a benzamidine-Sepharose column. Thrombin and benzamidin would be together in the eluate. Since they elute using benzamidine in a competitive elution then a complex of thrombin-benzamidine as in the present claims would have been formed.

Allary and Lorne do not teach using the other ingredients in the composition such as lysine, calcium chloride, NaCl, etc.

Hanada teaches that thrombin can be therapeutically viable using many of the other components in the composition and that p-aminobenzamidine and benzamidine are interchangeable, see all of col. 4.

Altshuler teaches that therapeutically viable thrombin can also include other components in the composition such as lysine, NaCl, glycerol, see col. 3, lines 13-30, example I.

Brezniak also teaches that therapeutically viable thrombin can include other ingredients in the composition such as calcium chloride, polyethylene glycol, NaCl, see abstract, page 847.

Thus, it would have been obvious to add the other components (NaCl, lysine, glycerol, calcium chloride, etc.) to the composition of thrombin and benzamidine of Allary and Lorne since it is well know in the art as is established by Altshuler, Brezniak and Hanada that the other components are well known to be added to therapeutically viable compositions of thrombin.

The percentages of activity of the enzyme are inherent to that enzyme, thus the conditions of the claims are inherent to the preparation. The same is true for the amount of sugar alcohol. The same ingredients are used in the preparations of the references as that which applicant uses, thus the inherent activities of the preparations will be the same.

Applicants argue that the since the board stated on page 7 of their decision that "[w]e do not, however, interpret the claim to require that the preparation be stable when stored in liquid form, or that it be virus-free, or that it be sterile" that now applicant is entitled to the present claims. This is not agreed with. After the board made the above quoted statement they also said, "[w]hile those properties may be desirable for a commercial product, the absence of such properties would not render the preparation

therapeutically ineffective. Therefore, they are not required by the phrase 'suitable for therapeutic purposes' when that phrase is given its broadest reasonable interpretation in light of the specification".

Thus, those characteristics do not impart patentability to the claims as applicant now suggests. And as stated above, those characteristics are inherent to the claimed composition and do not need to be explicitly stated by the references.

Applicant also argues that preparation without the added inhibitors do not have such great stability as claimed but the references do teach using the same exact inhibitors as applicant has.

Applicants argue that Lorne and Allary remove the inhibitors thus it cannot be the same preparation as claimed. Lorne and Allary teach a solution which contains the inhibitor and the enzyme. Applicant is claiming a "preparation" which is all the claims require. Applicant is **not** claiming a process. The claims read on a **product**. The same ingredients are in each. Thus, the same product as which is claimed is in the references which the board has agreed with the examiner on.

Thus, the same "preparation" as claimed is taught by the references.

Applicants continue to argue that the thrombin inhibitor was removed. They argue that only after it was removed it was used for practical use. While this is an interesting point, it does not negate the fact that the reference does teach the claimed invention. It may not teach that the final product is the claimed invention but it does teach the claimed invention. When the thrombin is on the column it contains the benzamidine, thus the combination of the two is taught by Allary and Lorne.

Applicant also argues that the references teach that benzamidine does not work well. This is not true. Benzamidine was noted as being a fine eluate and that the methyl ethyl arginine could also be used.

There is no evidence that the amount of sugar alcohol used would increase the viscosity of the thrombin preparation.

It is noted that this composition is a hemostatic (see Lorne, page 3, top) and that Lorne and Allary recognize that it can be used in a tissue glue making the preparation a constituent of a tissue glue.

Applicants also argue that Altshuler teaches that their solutions may not be stable beyond 8 months, but this is simply not true. First of all Altshuler is a secondary reference, not the primary reference, secondly, it clearly states in Altshuler that the formulations of Altshuler provide a stability of thrombin which is equivalent to at least an eighth month which would encompass 12 months, since 8 months is at least 12 months.

Next, applicant argues that EP 221700 teaches using high concentrations of polyols but first of all polyols are never claimed by applicant and secondly this reference was never even applied, so this comment by applicants is clearly improper.

Finally, applicants argue that claim 59 requires that the concentration of the polyol is 1-2 %, but polyols are not even claimed. Thus, this arguments is moot and without merit. Further, applicants do not even have support for "more than 70 %" as commented on above.

Applicant again argues that the references do not teach long term stability but that is inherent to the compositions formed by the combination of the references. The

combination of references teaches the same compositions as claimed by applicant, thus will have the same storage stability.

Applicants again turn to Altshuler and again misquote the teachings of this reference. It clearly states in Altshuler that the formulations of Altshuler provide a stability of thrombin which is equivalent to at least an eighth month which would encompass 12 months, since 8 months is at least 12 months and at least 12 months is at least 24 months and so on.

It is not clear why applicant argues EP 0221700 since that reference was not even part of this rejection.

Claims 49-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tripier et al. in view of Allary et al. or Lorne et al. and further in view of Hanada et al. and Altshuler.

Tripier teaches that thrombin, sodium chloride and benzamidine are all in the same thrombin formulation, see col. 9, lines 1-20.

Tripier does not teach that a sugar alcohol or p-aminobenzamidine is used in the formaulation or that the formulation is a constituent of a tissue glue.

Lorne and Allary use their composition as a tissue glue that have many of the same components and recognize that it can be used in a tissue glue making the preparation a constituent of a tissue glue and such as tissue glue would be considered to be a hemostatic (see Lorne, page 3, top).

Hanada teaches that thrombin can be therapeutically viable using many of the other components in the composition and that p-aminobenzamidine and benzamidine are interchangeable, see all of col. 4.

Altshuler teaches that therapeutically viable thrombin can also include other components in the composition such as lysine, NaCl, glycerol, see col. 3, lines 13-30, example I.

Thus, it would have been obvious to add glycerol to the composition of thrombin and benzamidine of Tripier since it is well know in the art as is established by Altshuler that glycerol is well known to be added to therapeutically viable compositions of thrombin and that Hanada establishes that p-aminobenzamidine and benzamidine are interchangeable in thrombin formulations.

The percentages of activity of the enzyme are inherent to that enzyme, thus the conditions of the claims are inherent to the preparation. The same is true for the amount of sugar alcohol. The same ingredients are used in the preparations of the references as that which applicant uses, thus the inherent activities of the preparations will be the same.

Applicant has simply dismissed Tripier as having the same deficiencies as the other references and provides nothing further except the same arguments as applied and addressed above. Tripier is clearly a good and pertinent reference for the reasons of record.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael V. Meller whose telephone number is 571-272-0967. The examiner can normally be reached on Monday thru Thursday: 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael V. Meller
Primary Examiner
Art Unit 1655

MVM